JACC Volume 13, No. 1
January 1989:143–4

Editorial Comment

Angiotensin-Converting Enzyme Inhibition for Congestive Heart Failure: Achievements and Potential*

EZRA A. AMSTERDAM, MD, FACC

Davis and Sacramento, California

Improved understanding of the pathophysiology of congestive heart failure has led to a major redirection of therapy for this condition during the past 15 years. Vasodilators (1) and diuretics (2) have been increasingly applied to improve deranged circulatory function through their beneficial effects on cardiac preload and afterload, replacing the traditional emphasis on positive inotropic therapy to augment impaired myocardial contractility. This therapeutic evolution is reflected in a current standard cardiology textbook (3) that, in contrast to prior editions, now places diuretics ahead of digitalis for treatment of cardiac failure.

Vasodilator therapy. The most striking change in the treatment of heart failure has been the widespread use of vasodilators to enhance cardiac performance without the disadvantage of increasing myocardial energy requirements (4). In addition to improvement of symptoms and function by vasodilator drugs (1), recent landmark studies have demonstrated that these agents can also reduce the drastic mortality rate of patients with heart failure. These salutary results have been achieved with hydralazine plus isosorbide dinitrate (5) and with the angiotensin-converting enzyme inhibitors enalapril (6) and captopril (7). Because of their unique physiologic actions, beneficial cardiac and extracardiac effects and favorable clinical results on symptoms, function and survival, the angiotensin-converting enzyme inhibitors are currently the subject of active investigation to further explore their therapeutic potential and indications in the treatment and possible prevention of left ventricular dysfunction and death.

Angiotensin-converting enzyme inhibitors in cardiac failure. Current findings indicate that there are a number of mechanisms by which the angiotensin-converting enzyme inhibitors may benefit patients with cardiac failure. The primary action of these drugs, attenuation of the activity of the renin-angiotensin-aldosterone axis (8), diminishes the availability of angiotensin II and aldosterone, potent hormonal mediators of vasoconstriction and renal sodium retention. The facilitatory role of angiotensin II on norepinephrine and vasopressin release is thus removed, and there is laboratory evidence that angiotensin-converting enzyme inhibition also stimulates vasodilator prostaglandin synthesis (9). These neurohumoral actions improve cardiac output and filling pressures (10,11), decreasing symptoms (10,12) and augmenting functional capacity (12). Additional clinical effects may contribute to the prolongation of survival by these drugs. Angiotensin-converting enzyme inhibition is associated with decreased frequency of ventricular arrhythmias (12) in cardiac failure, which may be related to reduced norepinephrine levels (10) and to maintenance of serum potassium (12). In experimental and clinical studies, captopril has protected against progressive postinfarction left ventricular functional (13,14) and morphologic (13–15) deterioration, with increased survival in animals (15) and humans (7).

Prophylactic use. These provocative results have stimulated interest in the potential prophylactic use of angiotensin-converting enzyme inhibitors for early asymptomatic left ventricular dysfunction, which is currently under investigation in the multicenter Survival and Ventricular Enlargement Study (14). Free radical scavenging has been proposed as a possible mechanism by which angiotensin-converting enzyme inhibitors may exert a cardioprotective effect. In in vitro studies it is independent of angiotensin-converting enzyme inhibitor activity and may be limited to agents with a sulfhydryl group such as captopril (16). Despite their impressive spectrum of salutary actions, the safe and effective use of angiotensin-converting enzyme inhibitors requires an awareness of their adverse effects, including hypotension, hyperkalemia and renal dysfunction.

Combined captopril-digoxin therapy. Although the clinical actions of angiotensin-converting enzyme inhibitors have been extensively investigated, certain practical aspects of their use have not been clarified. Thus, these agents, as well as other vasodilators, continue to be generally applied in conjunction with digitalis, but the utility of this combination has not been rigorously evaluated. In their extensive study in this issue of the *Journal*, Gheorghiade and colleagues (17) assess the separate and combined effects of captopril and digoxin in patients with moderate or severe cardiac failure (17). They found that the two agents had different and complementary effects that resulted in a greater improvement in hemodynamic function at rest and during exercise with their combined administration than with either one

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Cardiovascular Medicine, School of Medicine and Medical Center, Davis and Sacramento, California.

Address for reprints: Ezra A. Amsterdam, MD, 4301 X Street, Sacramento, California 95817.

0735-1097/89/$3.50

JACC Volume 13, No. 1
January 1989:143–4

given separately, thus providing a rationale for the use of both drugs in patients with heart failure. The value of this study to the clinician is enhanced by its inclusion of patients with generally marked cardiac failure who were evaluated by hemodynamic and neurohumoral data at rest and during exercise.

Certain limitations are inevitable in a study of this scope. As the authors acknowledge, the investigative protocol was not randomized or blinded and the short-term nature of the evaluation limits its application to long-term therapy. In addition, the two study groups differed in several important hemodynamic variables that may have accounted for some of the differences in results with captopril and digoxin. Nevertheless, the findings in this investigation extend our knowledge in an important area of clinical management and provide a stimulus for further research to clarify remaining questions.

References

1. Chatterjee K, Parmley WW. Vasodilator therapy for acute myocardial infarction and chronic congestive heart failure. J Am Coll Cardiol 1983;1: 133–53.
2. Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJC. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973;288: 1087–90.
3. Smith TW, Braunwald E, Kelly RA. The management of heart failure. In: Braunwald E, ed. Heart Disease. 3rd ed. Philadelphia: WB Saunders, 1987:485–529.
4. Amsterdam EA, Vera Z, Rendig S, Rutledge J, Miller RM. Nitroprusside therapy in cardiac failure: rationale, benefits, limitations. In: Julian DG, Wenger NK, eds. Management of Heart Failure. London: Butterworths, 1986:160–78.
5. Cohn J, Archibald DG, Ziesche S, et al. Effect of vasodilator on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative study. N Engl J Med 1986;314:1547–52.
6. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian enalapril survival study (CONSENSUS). N Engl J Med 1987;316: 1429–35.
7. Newman TJ, Maskin CS, Dennick LG. Effects of captopril on survival in patients with heart failure. Am J Med 1988;84:140–4.
8. Antonaccio MJ. Angiotensin converting enzyme (ACE) inhibitors. Ann Rev Pharmacol Toxicol 1982;22:57–87.
9. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. Circulation 1988;77:721–30.
10. DiCarlo L, Chatterjee K, Parmley WW, et al. Enalapril: a new angiotensin-converting enzyme inhibitor in chronic heart failure: acute and chronic hemodynamic evaluations. J Am Coll Cardiol 1983;2:865–71.
11. Halperin JL, Faxon DP, Creager MA, et al. Coronary hemodynamic effects of angiotensin inhibition by captopril and teprotide in patients with congestive heart failure. Am J Cardiol 1982;50:967–72.
12. The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
13. Sharpe N, Smith H, Murphy J, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988;1:255–9.
14. Pfeffer MA, Lamass GA, Vaughn DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. Engl J Med 1988;319:80–6.
15. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P. Survival after an experimental myocardial infarction: beneficial effects of long-term captopril. Circulation 1985;72:406–12.
16. Westlin W, Mullane K. Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? Circulation 1988; 77(suppl I):I-30–I-9.
17. Gheorghiade M, Hall V, Lakier JB, Goldstein S. Comparative hemodynamic and neurohormonal effects of intravenous captopril and digoxin, and their combinations in patients with severe heart failure. J Am Coll Cardiol 1989;13:134–42.